Table 5. Antithrombotic Therapy: Selected Clinical Data

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The clinical trials described in this table do not represent all the trials that the Panel reviewed while developing the recommendations for antithrombotic therapy. The studies summarized below are those that have had the greatest impact on the Panel's recommendations.

Methods	Results	Limitations and Interpretation
ATTACC/ACTIV-4a/REMAP-CAP: Multiplatform, Open-Label RCT of Therapeutic Anticoagulation in Noncritically Ill, Hospitalized Patients With COVID-19 in 9 Countries[1]		

Key Inclusion Criteria:
• Hospitalized with laboratory-confirmed SARS-CoV-2 infection without need for HFNC oxygen, NIV, MV, vasopressors, or inotropes
Key Exclusion Criteria:
• Discharge expected ≤72 hours
• Requirement for therapeutic anticoagulation or dual antiplatelet therapy
• High bleeding risk
Interventions:
• Therapeutic UFH or LMWH for 14 days or until discharge, whichever comes first (n = 1,190)
• SOC (n = 1,054)
Primary Endpoint:
• Organ support-free days at Day 21, evaluated on an ordinal scale
Key Secondary Endpoints:
• Survival until hospital discharge
• Hospital LOS
• Thrombosis or major bleeding
	Participant Characteristics:
	• Median age 59 years; 59% men; median BMI 30
	• 52% with HTN; 30% with DM; 11% with CVD
	• 66% required low-flow oxygen
	• D-dimer:
	  • 48.4% <2 times ULN
	  • 28.4% ≥2 times ULN
	  • 23.1% unknown
	• 62% on corticosteroids; 36% on RDV
	Primary Outcomes:
	• Organ support-free days: therapeutic anticoagulation superior to SOC (aOR 1.27; 95% CrI, 1.03–1.58; 99% posterior probability)
	• Survival until hospital discharge without organ support: 4% absolute difference favoring therapeutic anticoagulation arm (95% CrI, 0.5–7.2)
	• Outcome consistent across D-dimer stratum
	Secondary Outcomes:
	• Survival until hospital discharge: 92% in both arms
	• Hospital LOS: no difference between arms (aOR 1.03; 95% CrI, 0.94–1.13)
	• Thrombosis: 1% in therapeutic arm vs. 2% in SOC arm
	• Major bleeding: 2% in therapeutic arm vs. 1% in SOC arm
		Key Limitations:
		• Open-label study
		• Anticoagulation dose varied in SOC arm (27% received intermediate-dose thromboprophylaxis).
		• Studies had different criteria for ICU care and expected hospital LOS.
		• Only enrolled 17% of screened patients
		Interpretation:
		• Therapeutic heparin increased organ support-free days and decreased the number of patients requiring organ support.
		• Therapeutic heparin did not significantly affect hospital LOS or the number of major thrombosis events or deaths.
		• Major bleeds occurred 1% more frequently in therapeutic arm than in SOC arm.

Methods	Results	Limitations and Interpretation
RAPID: Open-Label RCT of Therapeutic Heparin in Moderately Ill, Hospitalized Patients With COVID-19 in 6 Countries[2]		

Key Inclusion Criteria:
• Hospitalized with COVID-19 and D-dimer ≥2 times ULN or any elevated D-dimer level and SpO_2 ≤93% on room air
• Hospitalized <5 days
Key Exclusion Criteria:
• Indication for therapeutic anticoagulation
• Dual antiplatelet therapy
• High bleeding risk
Interventions:
• Therapeutic UFH or LMWH for 28 days or until discharge or death (n = 228)
• Prophylactic UFH or LMWH for 28 days or until discharge or death (n = 237)
Primary Endpoint:
• Composite of ICU admission, NIV or MV, or death up to 28 days
Key Secondary Endpoints:
• All-cause death
• Mean organ support-free days
• VTE
• Major bleeding event
• Mean hospital-free days alive
	Participant Characteristics:
	• Median age 60 years; 57% men; mean BMI 30
	• 48% with HTN; 34% with DM; 7% with CVD
	• 91% had hypoxia; 6% received HFNC oxygen
	• D-dimer:
	  • 49% <2 times ULN
	  • 51% ≥2 times ULN
	• 69% on corticosteroids
	Primary Outcome:
	• ICU admission, NIV or MV, or death: 16% in therapeutic arm vs. 22% in prophylactic arm (OR 0.69; 95% CI, 0.43–1.10)
	Secondary Outcomes:
	• All-cause death: 2% in therapeutic arm vs. 8% in prophylactic arm (OR 0.22; 95% CI, 0.07–0.65)
	• Mean organ support-free days: 26 days in therapeutic arm vs. 24 days in prophylactic arm (OR 1.41; 95% CI, 0.9–2.21)
	• No difference between arms for VTE (1% in therapeutic arm vs. 3% in prophylactic arm) or major bleeding (1% in therapeutic arm vs. 2% in prophylactic arm)
	• Mean hospital-free days alive: 20 days in therapeutic arm vs. 18 days in prophylactic arm (OR 1.09; 95% CI, 0.79–1.50)
		Key Limitations:
		• Open-label study
		• Only enrolled 12% of screened patients
		Interpretation:
		• Compared to prophylactic heparin, therapeutic heparin reduced mortality (a secondary endpoint) but had no effects on the composite primary endpoint of ICU admissions or the need for NIV or MV, or death up to 28 days.
		• Major bleeding and VTE events were not different in the therapeutic and prophylactic arms.

Methods	Results	Limitations and Interpretation
HEP-COVID: Open-Label RCT of Therapeutic Heparin in High-Risk, Hospitalized Patients With COVID-19 in the United States[3]		

Key Inclusion Criteria:
• Hospitalized with supplemental oxygen
• D-dimer >4 times ULN or sepsis-induced coagulopathy score of ≥4
• Hospitalized <72 hours
Key Exclusion Criteria:
• Indication for therapeutic anticoagulation
• Dual antiplatelet therapy
• High bleeding risk
• CrCl <15 mL/min
Interventions:
• Therapeutic LMWH until hospital discharge or primary endpoint met (n = 129)
• Usual care of prophylactic or intermediate-dose LMWH until hospital discharge or primary endpoint met (n = 124)
Primary Endpoint:
• Composite of VTE, ATE, or death of any cause within 32 days of randomization
Key Safety Endpoint:
• Major bleeding
	Participant Characteristics:
	• Median age 67 years; 54% men; mean BMI 30
	• 60% with HTN; 37% with DM; 7% with CVD
	• 64% received oxygen via nasal cannula; 15% received high-flow oxygen or NIV; 5% received MV
	• 80% on corticosteroids
	Primary Outcomes:
	• Composite of VTE, ATE, and death within 32 days: 29% in therapeutic arm vs. 42% in usual care arm (relative risk 0.68; 95% CI, 0.49–0.96)
	  • Death: 19% in therapeutic arm vs. 25% in usual care arm (relative risk 0.78; 95% CI, 0.49–1.23)
	  • Thrombotic events: 11% in therapeutic arm vs. 29% in usual care arm (relative risk 0.37; 95% CI, 0.21–0.66
	• Non-ICU stratum composite of VTE, ATE, or death within 32 days: 17% in therapeutic arm vs. 36% in usual care arm (relative risk 0.46; 95% CI, 0.27–0.81)
	Safety Outcomes:
	• Major bleeding: 5% in therapeutic arm vs. 2% in usual care arm (relative risk 2.88, 95% CI, 0.59–14.02)
	• Non-ICU stratum major bleeding: 2% in both arms
		Key Limitations:
		• Open-label study
		• Only enrolled 2% of screened patients
		Interpretation:
		• Compared to usual care, therapeutic LMWH reduced the incidence of VTE, ATE, and death.
		• For patients not in the ICU, therapeutic LMWH significantly reduced thrombotic events and did not increase major bleeding.

Methods	Results	Limitations and Interpretation
ACTION: Open-Label RCT of Therapeutic Oral Anticoagulation (Rivaroxaban) in Hospitalized Patients With COVID-19 in Brazil[4]		

Key Inclusion Criteria:
• Hospitalized for COVID-19 with elevated D-dimer level
• Symptoms for ≤14 days
Key Exclusion Criteria:
• Indication for therapeutic anticoagulation
• CrCl <30 mL/min
• P2Y12 inhibitor therapy or aspirin >100 mg
• High bleeding risk
Interventions:
• Therapeutic anticoagulation for 30 days: rivaroxaban 15 mg or 20 mg daily; if clinically unstable, enoxaparin 1 mg/kg twice daily or UFH (n = 311)
• Usual care prophylactic anticoagulation with enoxaparin or UFH during hospitalization (n = 304)
Primary Endpoint:
• Hierarchical composite of time to death, hospital duration, and oxygen use duration through Day 30
Key Secondary Endpoints:
• Thrombosis, with and without all-cause death
• Mortality
• Bleeding events
	Participant Characteristics:
	• Median age 57 years; 60% men; mean BMI 30
	• 49% with HTN; 24% with DM; 5% with coronary disease
	• Critically ill: 7% in therapeutic arm; 5% in usual care arm
	• 75% required oxygen: 60% low-flow oxygen; 8% HFNC oxygen; 1% NIV; 6% MV
	• 83% on corticosteroids
	Primary Outcomes:
	• Composite of time to death, hospital duration, and oxygen use duration: no difference between arms (win ratio 0.86; 95% CI, 0.59–1.22)
	Secondary Outcomes:
	• No difference between therapeutic and prophylactic arms:
	  • Mortality: 11% vs. 8%
	  • Thrombosis: 7% vs. 10%
	• Any bleeding: 12% in therapeutic arm vs. 3% in usual care arm
	• Major bleeding: 3% in therapeutic arm vs. 1% in usual care arm
	• Clinically relevant, nonmajor bleeding: 5% in therapeutic arm vs. 1% in usual care arm
		Key Limitations:
		• Open-label study
		• Only enrolled 18% of screened patients
		• Longer duration of anticoagulation in the rivaroxaban arm (30 days) than the prophylactic anticoagulation arm (mean duration = 8 days)
		Interpretation:
		• When compared with usual care, therapeutic rivaroxaban did not reduce mortality, hospital duration, oxygen use duration, or thrombosis.
		• Patients who received therapeutic rivaroxaban had more clinically relevant nonmajor bleeding than those who received usual care.
		• The longer duration of therapy in the rivaroxaban arm may have influenced the difference in bleeding events.

Methods	Results	Limitations and Interpretation
REMAP-CAP/ACTIV-4a/ATTACC: Multiplatform, Open-Label RCT of Therapeutic Anticoagulation in Critically Ill, Hospitalized Patients With COVID-19 in 20 Countries[5]		

Key Inclusion Criteria:
• Hospitalized with severe COVID-19 and receiving HFNC oxygen, NIV, MV, ECMO, vasopressors, or inotropes
• Hospitalized <72 hours (ACTIV-4a, ATTACC) or <14 days (REMAP-CAP)
Key Exclusion Criteria:
• Discharge expected within 72 hours
• Requirement for therapeutic anticoagulation or dual antiplatelet therapy
• High bleeding risk
Interventions:
• Therapeutic UFH or LMWH for 14 days or until discharge, whichever comes first (n = 534)
• Usual care (n = 564)
Primary Endpoint:
• Organ support-free days at Day 21
Key Secondary Endpoints:
• Survival to hospital discharge
• Any thrombosis
• Composite of major thrombotic events or death
• Bleeding events
	Participant Characteristics:
	• Median age 60 years; 70% men; median BMI 30
	• 24% with chronic respiratory disease; 33% with DM; 10% with chronic kidney disease; 8% with severe CVD
	• 32% required HFNC oxygen; 38% required NIV; 29% required MV
	• 18% on vasopressors; 82% on corticosteroids; 32% on RDV
	Primary Outcome:
	• Median organ support-free days at Day 21: 4 days therapeutic arm vs. 5 days usual care arm (aOR 0.83; 95% CrI, 0.67–1.03; 99.9% posterior probability of futility; OR < 1.2)
	Secondary Outcomes:
	• No difference between therapeutic and usual care arms:
	  • Survival to hospital discharge: 63% vs. 65% (aOR 0.84; 95% CrI, 0.64–1.11)
	  • Thrombosis: 6% vs. 10%
	  • Major thrombotic events or death: 41% both arms
	  • Major bleeding events: 4% vs. 2% (aOR 1.48; 95% CrI, 0.75–3.04)
		Key Limitations:
		• Open-label study
		• Anticoagulation dose varied in usual care arm (i.e., 51% intermediate, 2% subtherapeutic, 5% therapeutic).
		• Inclusion criteria for hospital LOS and ICU-level care differed across trials.
		• Trial stopped for futility.
		Interpretation:
		• In patients requiring ICU care, therapeutic heparin did not reduce the duration of organ support or mortality.
		• Although the differences were nonsignificant, patients who received therapeutic anticoagulation had more bleeding events and fewer thrombotic events than patients who received usual care.

Methods	Results	Limitations and Interpretation
INSPIRATION: Open-Label RCT of Intermediate-Dose Versus Prophylactic-Dose Anticoagulant in Patients in Intensive Care With COVID-19 in Iran[6]		

Key Inclusion Criteria:
• Admitted to ICU
• Hospitalized <7 days
Key Exclusion Criteria:
• Life expectancy <24 hours
• Indication for therapeutic anticoagulation
• Overt bleeding
Interventions:
• Intermediate-dose anticoagulation: enoxaparin 1 mg/kg daily (n = 276)
• Prophylactic-dose anticoagulation (n = 286)
Primary Endpoint:
• Composite of adjudicated acute VTE, ATE, ECMO, or all-cause mortality within 30 days
Key Secondary Endpoints:
• All-cause mortality
• VTE
• Bleeding event
	Participant Characteristics:
	• Median age 62 years; 58% men; median BMI 27
	• 44% with HTN; 28% with DM; 14% with coronary artery disease
	• 32% required NIV; 20% required MV
	• 23% on vasopressors; 93% on corticosteroids; 60% on RDV
	Primary Outcome:
	• Composite adjudicated acute VTE, ATE, ECMO, or all-cause mortality: 46% in therapeutic arm vs. 44% in prophylactic arm (OR 1.06; 95% CI, 0.76–1.48)
	Secondary Outcomes:
	• No difference between therapeutic and prophylactic arms:
	  • All-cause mortality: 43% vs. 41%
	  • VTE: 3% both arms
	  • Major bleeding and clinically relevant nonmajor bleeding: 6.3% vs. 3.1% (OR 2.02; 95% CI, 0.89–4.61)
		Key Limitations:
		• Open-label study
		• Not all patients received ICU-level care.
		Interpretation:
		• Intermediate-dose anticoagulation did not significantly reduce VTE and ATE, the need for ECMO, or mortality.
		• Although the difference was nonsignificant, patients who received intermediate-dose anticoagulation had more bleeding events than patients who received usual care.

Key: ATE = arterial thromboembolism; BMI = body mass index; CrCl = creatinine clearance; CVD = cardiovascular disease; DM = diabetes mellitus; ECMO = extracorporeal membrane oxygenation; HFNC = high-flow nasal cannula; HTN = hypertension; ICU = intensive care unit; LMWH = low-molecular-weight heparin; LOS = length of stay; MV = mechanical ventilation; NIV = noninvasive ventilation; the Panel = the COVID-19 Treatment Guidelines Panel; RCT = randomized controlled trial; RDV = remdesivir; SOC = standard of care; SpO_2 = oxygen saturation; UFH = unfractionated heparin; ULN = upper limit of normal; VTE = venous thromboembolism

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